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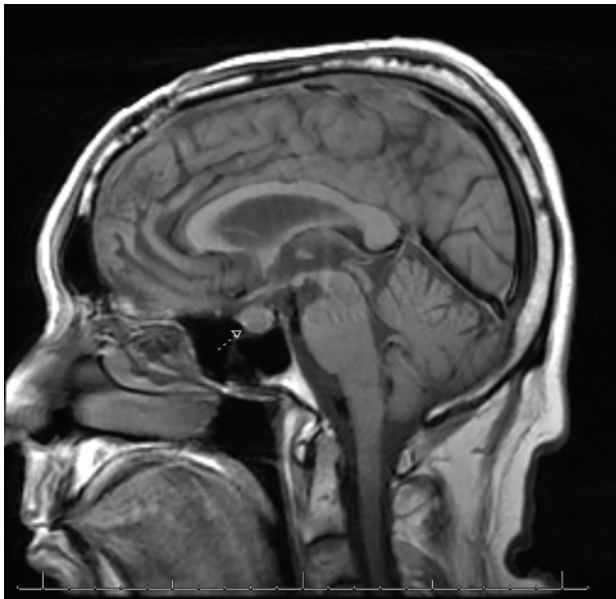
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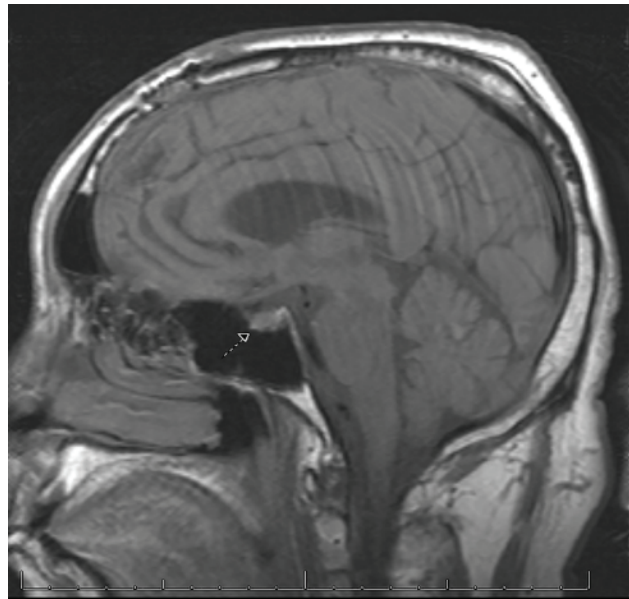
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# A Case of Ipilimumab Induced Hypophysitis

Eric Shiffrin, MD and Melinda Ukrainski, MD



**Figure 1.** Postcontrast T1-weighted magnetic resonance image of the brain two days prior to the fourth dose of ipilimumab and hospital admission, demonstrating diffuse enlargement of the pituitary gland (arrow).



**Figure 2.** Postcontrast T1-weighted magnetic resonance image of the brain three months before presentation and prior to starting ipilimumab, demonstrating normal pituitary gland architecture and size (arrow).

## INTRODUCTION

Ipilimumab (Yervoy®) is a human monoclonal antibody that has been shown to significantly improve survival in cases of metastatic melanoma.<sup>1</sup> Ipilimumab blocks cytotoxic T-lymphocyte antigen 4 (CTLA-4), a protein receptor on the surface of T-cells, resulting in their activation, proliferation and an anti-tumor response.<sup>2,3,4</sup> Commonly reported immune-related side effects of ipilimumab are enterocolitis, dermatitis, and hepatitis.<sup>5,6,7</sup> However, different endocrinopathies, including autoimmune hypopituitarism, have become emerging clinical entities in patients taking ipilimumab. We present a case of ipilimumab induced hypophysitis in a 62-year-old male presenting with fatigue and hypotension.

## CASE PRESENTATION

A 62-year-old male with a history of melanoma metastatic to the lung and brain status-post frontal craniotomy and whole brain radiation, as well as a recent diagnosis of hypothyroidism, presented from the oncology office with hypotension after receiving his fourth dose of ipilimumab

therapy. The patient had a routine blood pressure check after the chemotherapy infusion and was found to be hypotensive at 80/58 mmHg. He reported increasing fatigue over the past week. He denied chest pain, shortness of breath, dizziness and headache. He was given one liter of normal saline solution, but remained hypotensive and was directly admitted to the hospital.

On physical exam, the patient was tachycardic to 102 beats per minute with a regular rhythm, clear lungs, and positive orthostatics. Laboratory studies were significant for a thyroid stimulating hormone of <0.02 uIU/mL (normal range = 0.3 – 5 uIU/mL), free T4 of 1.2 ng/dL (normal range = 0.7 – 1.7 ng/dL), follicle stimulating hormone of 0.9 mIU/mL (normal range 1.5 – 12.4 mIU/mL), adrenocorticotrophic hormone (ACTH) of <9 pg/mL (normal range 9 – 46 pg/mL), total testosterone of 4 ng/dL (normal range 250 – 1100 ng/dL), and a free testosterone of 0.4 pg/mL (normal range 35 – 155 pg/mL). His white blood cell count, hemoglobin and electrolytes were within normal limits. A noon cortisol was 0.3 mcg/dL (normal A.M. range 16 – 20 mcg/dL and P.M. range 2 – 12 mcg/dL)

and a subsequent cosyntropin stimulation test with 250 µg of cosyntropin resulted in cortisol values of 5.4 mcg/dL and 8.8 mcg/dL at one hour and two hours respectively. An a magnetic resonance image (MRI) of the brain with and without contrast performed two days earlier for surveillance of his known brain metastases was reviewed on admission and revealed diffuse enlargement of the pituitary gland (Figure 1). This finding was new compared to an MRI performed three months earlier, prior to starting ipilimumab (Figure 2). The patient had no family history of endocrine disorders.

## DISCUSSION

Endocrine-related adverse events were reported in 8.5% of patients in a recent phase III trial designed to evaluate ipilimumab as an adjuvant therapy following resected stage III melanoma, with hypophysitis encompassing 5.1% of these events.<sup>8</sup> The majority of patients who develop hypopituitarism do so after the third or fourth dose of ipilimumab, suggesting a possible cumulative effect.<sup>1,3</sup> Adverse events have limited the duration of use of the drug in patients who could have clinical benefit from additional therapy.

The mechanism of hypopituitarism is likely from ipilimumab's immunomodulatory effect on activating T-cells, resulting in a lymphocytic hypophysitis.<sup>2,3,5,6</sup> It has also been shown that some pituitary cells express CTLA-4, the receptor target of ipilimumab.<sup>9</sup> Therefore, it remains unclear whether the adverse effects are caused by T-cells acting against antigens shared by tumor cells and normal cells or from a direct antibody effect on CTLA-4 receptors on pituitary cells, or both. Presenting symptoms are related to a pituitary mass effect and consequent hormone deficiencies.<sup>5,7,10</sup> Clinical manifestations may be non-specific as they depend on the extent of hormone deficiencies. Additionally, it is often difficult to recognize many of these symptoms in patients undergoing chemotherapy, but there should be a low threshold to consider hypophysitis in a patient taking ipilimumab. Typical symptoms include fatigue, headache, and loss of libido.<sup>10</sup> Other symptoms could include cold intolerance, visual disturbances, hypotension, hypoglycemia and hyponatremia. Our patient reported fatigue, but his diagnosis only became apparent after hypotension was noted.

MRI findings in ipilimumab-induced hypophysitis are non-specific and are typically characterized by a diffuse enlargement and homogeneous enhancement of the pituitary gland. Less commonly, heterogeneous enhancement has also been described.<sup>10-11</sup> While it is common to have radiographic evidence of hypopituitarism, a normal MRI is possible. Follow-up imaging often shows resolution of abnormal findings after hormone replacement.<sup>11</sup>

Pituitary hormone replacement with corticosteroids is critical to treatment, assuming ACTH is low. Either high dose or physiologic replacement dose corticosteroids are needed. Current recommendations advocate for high dose (1-2 mg/kg/day of prednisone or equivalent) steroids for moderate to life threatening symptoms.<sup>12</sup> However, it is not clear whether initial high doses of corticosteroids are beneficial in treating hypophysitis. While they may play a role in reducing inflammation, they do not improve neuro-endocrine function compared to physiologic doses. However, high doses of corticosteroids may increase morbidity through side effects.<sup>3,13</sup> Mineralocorticoid replacement is not needed since the renin-angiotensin-aldosterone system is still intact. It should be at the discretion of the oncologist and endocrinologist as to whether ipilimumab should be continued based on the condition of the patient and response to hormone replacement. Hormone deficiencies can improve, although corticotroph function seems to be the least likely to recover.<sup>14</sup> Many doctors recommend close monitoring for hormone abnormalities in patients receiving ipilimumab, especially after the third infusion.

## KEY POINTS

Hypophysitis is a well recognized side effect of ipilimumab therapy. A high clinical suspicion for hypopituitarism in patients receiving the drug is imperative due to the non-specific symptoms and potentially life threatening consequences. Corticosteroids should be promptly initiated as soon as secondary adrenal insufficiency is detected. While ipilimumab has many side effects, the drug has improved survival in metastatic melanoma and remains an important treatment option.



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